

## REMARKS

### Claim Status

Claims 184-201 are pending, with elected claims 184-186 presented for examination.

### General Comments

Applicant submits this response in an effort to clarify the cited literature, particularly the Timko reference (WO 00/67558), which is central to the remaining rejections. Specifically, there is an issue over, first, whether Timko actually discloses tobacco plants with increased nicotine and, second, whether in any event it would have been obvious to use such increased nicotine plants to produce cigarettes having desirable tar-to-nicotine ratios and pH.

On the first point the PTO contends that Timko “implicitly” discloses tobacco plants with increased nicotine. Office Action, page 2. In other words, while admitting that “Timko *et al.* do not explicitly state the phrase ‘tobacco plants with increased nicotine,’” the PTO points to Timko’s alleged disclosure of “plant promoter regions that are capable of conferring high levels of transcription” and “coding sequences for PMT genes.” *Id.*, pages 2-3. “Therefore,” according to the PTO, “Timko *et al.* disclose conferring high levels of transcription of PMT (i.e. over expression of PMT) and as a result, higher levels of nicotine.” *Id.* at page 2. Further, the PTO alleges that “Timko *et al.* compare low nicotine mutants with the engineered tobacco plants with transcripts encoding PMT, thus showing that increased nicotine plants were created . . . (pages 29-30).” *Id.*

At the outset, however, Timko does not genetically engineer or overexpress any sequence to produce transgenic tobacco plants with increased nicotine. Thus, it is unclear what the PTO refers as “engineered tobacco plants with transcripts encoding PMT.”

While Timko may disclose PMT coding sequences, nowhere does the reference disclose or even hint at overexpressing PMT to produce tobacco plants with increased nicotine levels. The “HP” plants to which the low nicotine mutants are compared are conventional wild-type tobacco (i.e., **not** engineered plants) with normal levels of PMT

expression and nicotine synthesis. Contrary to the PTO's stated position, therefore, Timko does not disclose tobacco plants with increased expression of PMT or increased nicotine.

Furthermore, Timko does not disclose promoters "that are capable of conferring high levels of transcription." Excluding the ADC2 promoter, Timko's promoters are PMT promoters that already control PMT expression in the wild type plant. Thus, Timko's PMT promoters do not confer high nicotine expression levels. Moreover, Timko demonstrates that the ADC2 promoter confers lower levels of expression than PMT promoters. Accordingly, Timko neither teaches nor suggests any promoter that can be used to provide higher levels of PMT expression than that already occurring in the wild type plant. To the contrary, consistent with his published finding, Timko postulates that using the disclosed promoters confers a level of transcription similar to that of PMT in the wild type.

However, except for the ADC2 promoter, the promoters disclosed are PMT promoters that already control expression of PMT coding sequences in the wild type plant. Data in Timko show that the ADC2 promoter provides lower levels of expression than PMT promoters.

Without the basic starting material, *i.e.*, without increased nicotine plants, no reasonable combination of Timco with the other cited references could have suggested genetically engineering tobacco for a cigarette with increased nicotine and a desirable tar-to-nicotine ratio.

### **Rejections under 35 U.S.C. § 103**

#### **A. Claims 184 and 185**

Claims 184 and 185 are rejected over Perkins *et al.* (USPN 3, 861,400) in view of Newton *et al.* (USPN 3,957,060), Timko (WO 00/67558), Russell (Nicotine and Public Health, 2000), and Gibson (USPN 3,878,850). Office Action, item 9, pages 4-6.

Specifically, the PTO alleges that "Perkins *et al.* disclose cigarettes with a tar to nicotine ratio between 3 and 8 and that the pH of the smoking material should be kept below approximately 6.5." *Id.* at page 4. Yet, the PTO admits that "Perkins *et al.* do not disclose

that the tar to nicotine ratio was measured by FTC or ISO methods, the use of transgenic *Nicotiana tabacum* to supply nicotine, or that the pH of the cigarette smoke produced has a pH of 6.5 or lower.” *Id.* at page 5. However, the PTO alleges “Perkins *et al.* teaches the general concept of increased tar to nicotine ratio, and it would have been obvious to one of ordinary skill in the art at the time of invention to manipulate the tar to nicotine ratio to produce a cigarette with low tar and medium nicotine.” *Id.*

Because Perkins does not disclose transgenic *Nicotiana tabacum* to supply nicotine, the PTO invokes Timko *et al.*, alleging “Timko *et al.* teach the engineering of *Nicotiana tabacum* to produce higher levels of nicotine using a heterologous coding sequence (nucleic acid encoding PMT) to boost levels of putrescine N-methyltransferase (PMT) which is an enzyme whose presence is a rate limiting step in supplying a compound for nicotine synthesis in tobacco and thus increasing the production of nicotine.” *Id.* In so doing, the PTO alleges it would have been obvious “to use the tobacco of Timko *et al.*, which has higher levels of nicotine, in place of the added nicotine salts and compounds disclosed by Perkins *et al.* to produce a cigarette with the tar to nicotine ratios suggested by Perkins *et al.* and Russell. Doing so would have lead to predictable results (higher nicotine) and lower tar.” *Id.* at pages 5-6.

The PTO cites Gibson for disclosing “a choky flavor is associated with an alkaline trend in pH of smoke” and Russell for disclosing specific tar to nicotine ratios. *Id.* at page 6.

Combining the five references, the PTO alleges that it “would have been obvious to make the cigarette of Perkins *et al.* with the tobacco of Timko *et al.*, and adjust the pH to lower than 6.5 by the methods and materials of Gibson *et al.* if the pH of the smoke produced was alkaline in nature or produced “choky” flavor.” *Id.* Applicants respectfully traverse the grounds for this rejection.

In order to validate a conclusion that a claim would have been obvious, the PTO must show that all recited elements of the claim were evidenced in the art. Further, the PTO must demonstrate that one of ordinary skill in the art could have combined the elements in the manner claimed, via known methodology, with no change in the respective function(s) of the

elements and with the resultant combination yielding nothing more than predictable results. *KSR v. Teleflex*, 127 S. Ct. 1727, 1739 (2007).

If any of these requirements does not pertain, then the PTO is barred from concluding that the claim in question would have been obvious. Such is the case here because no reasonable combination of the references could have led the skilled artisan to a cigarette comprising a portion of an increased-nicotine transgenic *Nicotiana tabacum* plant, where the cigarette is characterized by (i) a tar-to-nicotine yield ratio of between about 3 and about 8, as measured by the FTC or ISO method, and (ii) cigarette smoke having a pH of about 6.5 or lower.

Applicant and PTO agree that the primary reference, Perkins, discloses adding exogenous nicotine to increase the nicotine content of a smoking product. That is, Perkins teaches adding nicotine pectinate or nicotine alginate to reconstituted tobacco or a non-tobacco substitute material to increase the nicotine content of the resultant smoking product. In sharp contrast, the instant tobacco itself has increased nicotine content without exogenous nicotine. Through genetic engineering, therefore, applicant removed the need for adding external nicotine sources to tobacco thereby facilitating cigarettes with increased nicotine and desirable tar-to-nicotine ratios.

As discussed above, the PTO understands Timko to produce increased nicotine tobacco plants. Office Action, page 2. However, and as explained above under “General Comments,” Timko does not genetically engineer or overexpress any sequence to produce transgenic tobacco plants with increased nicotine. In fact, nowhere does Timko teach or suggest tobacco with “higher [than normal] levels of nicotine. To the contrary, the tobacco with “higher” nicotine in Timko is wild-type tobacco with levels of nicotine that are “higher” than the levels in low nicotine mutants, but the same, not higher, than convention tobacco.

Because Timko thus neither teaches nor suggests a transgenic, increased-nicotine *Nicotiana* plant, one could not have merely “substitute[d]” Perkin’s tobacco cigarettes with Timko’s tobacco, thereby producing a product having increased nicotine, as presently claimed. For this reason alone, the rejection is improper and should be withdrawn.

Because Timko does not provide increased nicotine tobacco, as the PTO posits, it appears the PTO bases its rejection on improper hindsight reconstruction. That is, the PTO improperly harnesses applicant's own specification to "reconstruct" applicant's own claimed cigarette. Such hindsight reconstruction can not be used for establishing obviousness, as the Federal Circuit has made clear that "Obviousness is determined as a matter of foresight, not hindsight." *KSR* at 421. Thus, for this reason alone, the rejection is improper and should be withdrawn.

In the absence of any evidence of record to the contrary, moreover, the PTO has not established that Perkin's tobacco product is essentially equivalent and thus amenable to substitution with Timko's tobacco. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicants' disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *See MPEP § 2144.06.* Here, the PTO provides neither evidence nor explanation for establishing any equivalency between Perkin's tobacco product and Timko's tobacco, let alone any reason for such substitution.

Even if the PTO had proffered rationale for equivalency between Perkin's tobacco product and Timko's tobacco, such rationale would surely fall short because Timko does not disclose tobacco plants overexpressing PMT with increased nicotine. That is, while Timko discloses PMT coding sequences, no where does Timko disclose "overexpressing" PMT to produce tobacco plants with increased nicotine levels. In fact, none of Timko's promoters confer elevated PMT levels, compared to wild-type PMT levels.

Contrary to the PTO's position, therefore, Timko does not disclose tobacco plants with increased nicotine. By the same token, no permutation of teachings reasonably gleaned from the cited art could have suggested genetically engineering tobacco for smoking articles having increased nicotine and decreased tar-to-nicotine ratio. Since the cited references therefore do not establish a *prima facie* case of obviousness, the rejection should be withdrawn.

## B. Claim 186

Claim 186 is rejected over Perkins *et al.* (USPN 3, 861,400), Newton *et al.* (USPN 3,957,060), Timko (WO 00/67558), Russell (Nicotine and Public Health, 2000), and Gibson (USPN 3,878,850), and in further view of Conkling *et al.* (USPN 6,423,520). Office Action, item 16, pages 6 and 7.

The PTO alleges “Timko *et al.* discloses uses genetic engineering to increase expression or production of PMT, but do not disclose up-regulating quinolate phosphoribosyl transferase (QPT or QPRTase).” *Id.* at page 7. The PTO relies on Conkling for “creating a transgenic *Nicotiana* having increased QPRT expression when compared to altering the expression of QPRTase by using complimentary nucleic acid sequences encoding a segment of QPRTase (abstract).” *Id.*

Combining the references, the PTO alleges “it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Timko *et al.* and Conkling *et al.* to increase production of the two different, known, rate limiting enzymes in the production of nicotine, and thus increasing nicotine production in transgenic plants that result from genetic manipulation.” *Id.* at page 7.

Applicant traverses the grounds for this rejection. As discussed above, no reasonable combination of the primary references suggests genetically engineering tobacco as an approach to producing a cigarette with increased nicotine and a desirable tar-to-nicotine ratio. That is, because none of the cited references discloses increased nicotine plants, the primary references cannot render the present claims obvious, within the meaning of Section 103.

Conkling does not remedy these admitted deficiencies because Conkling likewise fails to suggest a cigarette made from genetically engineered tobacco with increased nicotine content. Accordingly, no permutation of the cited references could render the present claims obvious under Section 103, and the rejection therefore should be withdrawn.

## CONCLUSION

Applicant believes the application is in condition for allowance, and requests an early indication of same. Examiner is invited to telephone the undersigned if an interview would advance prosecution.

Respectfully submitted,

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**The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of the relevant fee(s) from the deposit account.**